Childhood-Onset Schizophrenia: Biological Markers in Relation to Clinical Characteristics

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Objective: *The purpose of this study was to examine the relationships between clinical and neurobiological measures of childhood-onset schizophrenia. It was hypothesized that there would be a more striking pattern in the rare cases with very early onset than is seen in subjects with later onset.* *Method:* *Premorbid, clinical, prenatal, perinatal, and magnetic resonance imaging brain measures were examined in 29 children and adolescents who met the DSM-III-R criteria for schizophrenia with onset before age 12. Specifically, gender, premorbid adjustment, and clinical symptoms were examined in relation to cerebral volume, ventricular volume, and maternal obstetrical complications.* *Results:* *Males were more likely to have had an insidious onset than females. There was a significant negative correlation between score on the Scale for the Assessment of Negative Symptoms and total cerebral volume.* *Conclusions:* *These neurobiological associations support the continuity of early-onset schizophrenia with the later-onset disorder; the striking association between smaller cerebral volume and negative symptoms suggests a more homogeneous or more potent neurobiological basis for very early-onset schizophrenia.*
(Am J Psychiatry 1997; 154:64–68)

The study of childhood-onset schizophrenia provides a unique opportunity for understanding schizophrenia, since patients with early onset may represent a more homogeneous group, one with a more salient early brain lesion and/or unique or more potent risk factors responsible for early activation of the illness (1–3). Very early-onset schizophrenia is rare, having at most one-fiftieth the treated prevalence of the later-onset disorder. Indirect evidence for greater neurodevelopmental insult in patients with very early onset has been suggested by their more disturbed premorbid histories relative to the histories of patients with later onset, including clinically significant prepsychotic speech and language disorders and, for a subgroup of males, transient premorbid features of pervasive developmental disorders. In addition, insidious onset of psychosis with a chronic unremitting course is the rule (1, 4–6).

An ongoing brain magnetic resonance imaging (MRI) study of childhood-onset schizophrenia at the National Institute of Mental Health (NIMH) has supported continuity with the adult-onset disorder (7). In that study, the initial group of 21 patients with childhood-onset schizophrenia were found to have smaller cerebral volumes ($p=0.002$) and larger lateral ventricular volumes ($p=0.06$) than healthy control subjects, although temporal lobe volumes appeared to have been relatively spared (8). In the initial study it was also found that the effect size (calculated from z scores) of smaller cerebral volume in the group with childhood-onset schizophrenia tended to be more striking than in adult-onset cases ($p=0.06$). The addition of MRI data from seven more cases now results in a significantly larger effect size of smaller cerebral volume than that reported for adult-onset disorder ($p=0.01$, unpublished data of J.L. Rapoport, June 1996).

Other measures of risk, including ratings of prenatal and perinatal events, were also obtained as part of the NIMH study. However, the relationships among clinical features of childhood-onset schizophrenia and neurobiological indexes including gender, maternal obstetrical risk, and MRI anatomic brain measures have not been examined in any study to date.

There is a sizable literature documenting clinical/biological relationships in later-onset schizophrenia. For example, with some important exceptions (9–11), males have poorer premorbid adjustment, earlier age at onset, more negative symptoms, histories of more obstetrical complications in the mother, and more structural brain abnormalities (12, 13). In addition, enlarged ventricles have been linked to poor premorbid course (14), earlier age at onset (15), and higher ratings on negative symptoms (16, 17), although again these findings have not been universally replicated (18–20).

Total cerebral volume has been found to be signifi-

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The authors thank Charles T. Gordon, M.D., Kathleen McKenna, M.D., and Leslie K. Jacobsen, M.D., for their help with the study and Alan Brier, M.D., and F. Xavier Castellanos, M.D., for their comments.

cantly decreased in adults with schizophrenia (19), and decreased volume has been reported to be significantly correlated with impairment in neuropsychological functioning (21) and with negative family history of schizophrenia (22). There are only a few studies addressing the relation between total brain volume and symptom severity. These studies (23, 24)—one a postmortem study—found a significant correlation between negative symptoms and decreased total cerebral volume. This little-noticed finding seems to be important, since primary negative or deficit symptoms are thought to be the core manifestations of the developmental abnormalities in schizophrenia (25) and may be associated with earlier age at onset (26, 27). MRI abnormalities have also been associated with maternal obstetrical complications (15), again with exceptions (28); other correlates with obstetrical complications have been more controversial, since higher rates of complications have been only inconsistently associated with early age at onset and/or male gender (15, 29).

In the present study, gender, premorbid adjustment, and clinical symptoms were examined in relation to cerebral and ventricular volumes and maternal obstetrical complications in a unique sample of 29 subjects with childhood-onset schizophrenia. At issue was whether a stronger or more consistent pattern of correlates emerged relative to that reported for adults. As reported previously (4), 28% and 33% of the patients had had features of pervasive developmental disorders and language disorders, respectively, before the onset of psychosis. Language milestones and the presence or absence of autistic features were also examined in relation to obstetrical and brain measures. We hypothesized a more striking relationship among these measures in comparison with that reported in studies of adults.

METHOD

From over 600 initial referrals, 138 potential subjects were selected for in-person screening, of whom 34 were diagnosed as having schizophrenia with onset on or before age 12 (30). Of these, 29 children and adolescents who met the DSM-III-R criteria for schizophrenia (mean age at onset=10.2 years, SD=1.5, range=10–19), participating in an ongoing double-blind clozapine trial, were chosen as the subjects for the present analyses. Following extensive chart review by two psychiatrists (J.A. and J.A.F.), all participants underwent a comprehensive screening process, as well as a series of biological measures. All had had educational and developmental achievement and/or cognitive test results commensurate with an IQ of 70 or above before the onset of psychosis. This was true even for the subjects who had had premorbid speech/language disorders or transient features of pervasive developmental disorders. The mean full-scale IQ before admission to NIMH of the 27 subjects with available IQ tests or estimated scores was 84.6 (SD=18.9).

After the study was explained, assent was obtained from the subjects and written informed consent was obtained from the parents. The protocol was approved by the NIMH institutional review board. More complete descriptions of this ongoing study are available elsewhere (3, 4, 7, 30, 31).

Language development, as determined by age at first sentence, was assessed through interviews with parents and the corresponding section of the Autism Diagnostic Interview (32). Premorbid functioning was rated with the Premorbid Adjustment Scale (33). Premorbid speech and language disorders as defined by DSM-III-R criteria were determined with the use of psychological reports, school records, and prior hospital records. Selected parts of the Autism Diagnostic Interview (communication, social development and play, interests, and behaviors), clinical interviews, and all available medical charts and records were used to rate autistic symptoms (features or full syndrome of pervasive developmental disorders). Type of onset was classified by the two rating psychiatrists as subacute (6 months or less from baseline to change, i.e., from initial nonspecific symptoms to first psychotic symptoms) or insidious (more than 6 months from baseline to first psychotic symptoms) on the basis of all available information, including parent interviews, school reports, and hospital records. Reliabilities were excellent for ratings on the Premorbid Adjustment Scale, speech/language disorders, and symptoms of pervasive developmental disorders, with kappas or intraclass correlation coefficients ranging from 0.89 to 1.00 (4). The reliability for type of onset, however, was only fair (kappa=0.41).

TABLE 1. Clinical Ratings and Biological Measures of Subjects With Childhood-Onset Schizophrenia

Variable	N[a]	Mean	SD	Range
Total cerebral volume (ml)	28	1036.35	119.34	844–1276
Total ventricular volume (ml)	28	16.01	7.45	5.85–30
Premorbid Adjustment Scale score	29	2.30	1.59	0–4.60
Age at first sentence (months)	28	25.39	7.93	6–36
BPRS total score	28	80.40	15.05	38.50–102
SANS total score	29	17.96	4.89	7–25
SAPS total score	29	13	4	4–19
Research Obstetrical Scale total score	25	2.08	2.17	0–9

[a]N varies because of missing data on some variables for some subjects.

Ratings on the Brief Psychiatric Rating Scale (BPRS) (34), the Scale for the Assessment of Negative Symptoms (SANS) (35), and the Scale for the Assessment of Positive Symptoms (SAPS) (36) were also obtained for all subjects during the fourth week of the drug-free period of the clinical trial, before the patients were randomly assigned to a neuroleptic, and these were used in the correlational analysis. Interrater reliability was 0.91 for the BPRS, 0.89 for the SANS, and 0.92 for the SAPS.

The history of maternal obstetrical complications for each patient was obtained from obstetrical records (N=20 of 29) and from a detailed questionnaire, completed by all of the biological mothers (N=25), covering prenatal and perinatal events. These charts and interviews were scored with the Research Obstetrical Scale (37). Total scores derived from the subscales (prenatal, delivery, and infancy) were used for the analysis.

All subjects underwent brain scans with the same General Electric 1.5-T Signa scanner, located at the National Institutes of Health Clinical Center. A three-dimensional, spoiled gradient recall acquisition in the steady state imaging sequence (TE=5 msec, TR=24 msec, flip angle=45°, acquisition matrix=192×256 pixels, number of excitations=1, field of view=24 cm) was used to obtain T_1-weighted images with a slice thickness of 1.5 mm in the axial and sagittal planes and 2.0 mm in the coronal plane.

A novel image analysis technique, which utilizes an active surface template of the brain to incorporate prior knowledge of brain anatomy (38), was used to ascertain total cerebral volume. This method models the brain surface as an elastically deformable structure while using successive iterations of an energy minimization function to enforce constraints on curvature and topology. After this procedure, the brain images were edited in the axial plane, slice by slice, by experienced raters to remove remaining artifacts such as eyeballs or patches of dura mater. Intraclass correlations for the volumes of the edited brain images were 0.99 for interrater reliability and 0.95 for the comparison with volumes derived from more conventional slice-by-slice tracing (31, 39).

Lateral ventricular volumes were calculated by summing area measurements from all coronal slices on which ventricles were visible

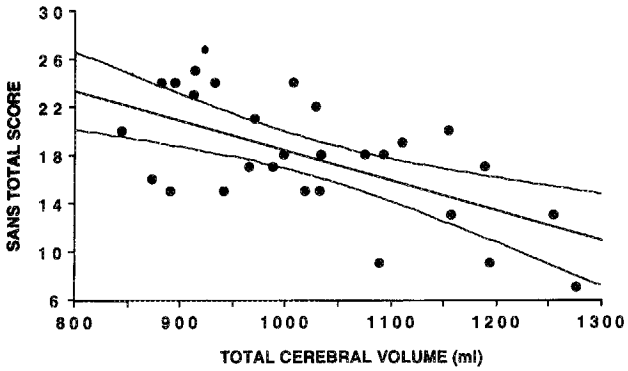
TABLE 2. Correlations Among Clinical and Biological Variables of Subjects With Childhood-Onset Schizophrenia

Variable	Total Cerebral Volume						Total Ventricular Volume						Research Obstetrical Scale Total Score					
	Males		Females		Total Group		Males		Females		Total Group		Males		Females		Total Group	
	r	N[a]	r	N[a]	r	N[a]	r	N[a]	r	N[a]	r	N[a]	r	N[a]	r	N[a]	r	N[a]
Premorbid Adjustment Scale score	0.16	15	–0.08	14	0.17	29	0.19	15	0.02	14	0.13	29	0.25	15	–0.21	10	–0.14	25
Age at first sentence	–0.11	14	–0.32	14	–0.20	28	0.32	14	0.02	14	0.14	28	0.19	14	–0.21	10	0.19	24
BPRS total score	–0.66*	13	0.25	13	–0.10	26	–0.19	13	–0.23	13	–0.19	26	0.19	14	0.29	10	0.21	24
SANS total score	–0.70**	14	–0.36	14	–0.65***	28	0.14	14	0.10	14	0.07	28	–0.26	15	0.37	10	–0.21	25
SAPS total score	–0.61*	14	–0.01	14	–0.37	28	–0.07	14	–0.31	14	–0.21	28	0.04	15	0.21	10	–0.04	25
Research Obstetrical Scale total score	0.16	14	–0.21	10	0.28	24	0.28	14	–0.02	10	0.25	24						
Subacute onset of illness	–0.23	15	–0.09	14	0.11	29	0.06	15	0.44	14	0.28	29	0.08	15	–0.42	10	0.20	25
Presence of pervasive developmental disorders	–0.34	15			0.27	29	0.19	15			0.18	29	–0.01	15			0.14	25
Presence of premorbid language disorders	–0.60*	15	–0.09	14	–0.04	29	0.05	15	–0.02	14	0.06	29	0.07	15	0.08	10	0.15	25

[a]N varies because of missing data on some variables for some subjects.

*p=0.01. **p=0.004. ***p<0.001.

FIGURE 1. Correlation Between Total Cerebral Volume and Total Negative Symptoms (Scale for the Assessment of Negative Symptoms) of Subjects With Childhood-Onset Schizophrenia[a]



[a]The middle line represents the regression, and the top and bottom lines represent the 95% confidence interval. The correlation between total cerebral volume and SANS score was significant (r=–0.65, N=28, p<0.001).

with the use of an operator-supervised thresholding technique that required little subjectivity. The intraclass correlation for ventricular volumes was 0.99. Further details are provided elsewhere (7, 31, 39).

All statistical analyses used SAS (version 6.07) or BMDP (1990 revision) statistical packages. Chi-square and t tests were used to examine gender differences within the study group. Pearson correlations were obtained for premorbid/clinical and biological variables. The correlations for males and females were contrasted by using Fisher's r-to-z test. A stepwise multiple regression was used to determine which of the premorbid/clinical and MRI variables accounted for the variance in SANS, SAPS, and BPRS scores; 0.05 was taken as the significance level for these analyses. All p values were two-tailed; 0.01 was taken as the significance level for correlational data because of the number of correlations performed.

RESULTS

Males and females did not differ significantly in terms of premorbid functioning. Given the higher rate of pervasive developmental disorders in males, it is not surprising that all of the subjects who had had partial- or full-syndrome pervasive developmental disorders (N=7) were male (χ^2=9.5, df=1, p=0.002). Males were also more likely to have had an insidious onset of psychosis (χ^2=6.6, df=1, p=0.07). There were no significant differences between males and females on the other measures examined in the study. The ratings on the measures are shown in table 1.

While a total of 29 schizophrenic patients have been seen to date, data on individual measures are missing for some patients, so that the numbers vary from 24 to 29 for individual measures (tables 1 and 2). On the basis of reports on adult patients as well as the developmental measures that were uniquely abnormal for our pediatric group, we planned to test 27 correlational relationships between clinical measures, MRI measures, and total obstetrical complications. Since these were carried out for the whole study group and for males and females separately, a total of 75 correlations were examined for this analysis. The three sets of correlational data are shown in table 2. A total of five correlations were significant, all in the expected direction. Four were significant for males alone, and one was significant for the total group.

For the whole group, total cerebral volume showed a significant negative relationship with total score on negative symptoms (SANS) (figure 1). In the stepwise multiple regression, total cerebral volume accounted for 31% of the variance in SANS score (p=0.004). (No variables met the significance level of 0.05 in the stepwise multiple regression for the SAPS and the BPRS.)

After covariance for IQ, the significant association between smaller total cerebral volume and negative symptoms was virtually unchanged (r=–0.64, p=0.002). When correlational patterns were examined for males and females separately, no relationships were significant for females. For males, smaller cerebral volume was significantly associated with SANS score, SAPS

score, the presence of language disorders, and higher scores on the BPRS (table 2). However, correlations for males and females did not differ significantly by Fisher's r-to-z test.

DISCUSSION

This report represents the only examination to date of neurobiological measures in relation to clinical features in childhood-onset schizophrenia. While the ratings of maternal obstetrical complications were not collected in a blind or controlled fashion, the rarity of the study group and the potential importance of the question of these complications make this preliminary analysis worth sharing. A few significant relationships among premorbid, clinical, obstetrical, and brain MRI measures were seen. Given the fact that a modest proportion of the variance in human intelligence (between 12% and 31%) may be accounted for by the size of cerebral structures (40), the strong association between smaller cerebral volume and negative symptoms in our study, even after covariance for IQ, is striking. Our findings support the few studies (23, 24) that found a significant association between smaller brain size and negative symptoms in adult schizophrenia, but our data show a more striking relationship. Moreover, other studies of adults (41, 42) have not found such a relationship. Finally, the observation that negative symptoms are more frequently seen in early-onset schizophrenia (26, 27) makes this finding particularly intriguing.

The strong premorbid evidence for more disrupted early brain development, a more chronic unremitting course, and the treatment-refractory nature of our study group (4) may be related to this stronger relationship between smaller total cerebral volume and negative symptoms. This is consistent with our MRI findings of continuity in the pattern of subtle brain abnormalities, with evidence for a greater effect size of differences in total cerebral volume (7).

These conclusions are tentative because of the obvious limitations of the study, such as the small size of our study group and the unknown selection and ascertainment biases inherent in the study of any rare entity (4). The gender-specific differences in correlational patterns are also difficult to interpret, since these did not reach significance.

Our finding is particularly interesting in light of the recent conceptualization of schizophrenia as a general cortical disorder (43). While smaller total cerebral volume is likely to be nonspecific, representing a secondary, common brain response and not a primary pathophysiologic event (44), this finding together with unpublished observations of higher rates of mental retardation in siblings, suggests a general pattern of brain maldevelopment for this study group. More detailed studies of regional gray matter in these patients as well as studies of brain development during adolescence are ongoing.

REFERENCES

1. Russell AT, Bott L, Sammons C: The phenomenology of schizophrenia occurring in childhood. J Am Acad Child Adolesc Psychiatry 1989; 28:399–407
2. Asarnow JR: Annotation: childhood-onset schizophrenia. J Child Psychol Psychiatry 1994; 35:1345–1371
3. Gordon CT, Frazier JA, McKenna K, Giedd J, Zametkin A, Zahn T, Hommer D, Hong W, Kaysen D, Albus KE, Rapoport JL: Childhood-onset schizophrenia: an NIMH study in progress. Schizophr Bull 1994; 20:697–712
4. Alaghband-Rad J, McKenna K, Gordon CT, Albus KE, Hamburger SD, Rumsey JM, Frazier JA, Lenane MC, Rapoport JL: Childhood-onset schizophrenia: the severity of premorbid course. J Am Acad Child Adolesc Psychiatry 1995; 34:1273–1283
5. Hollis C: Child and adolescent (juvenile onset) schizophrenia: a case-control study of premorbid development impairment. Br J Psychiatry 1995; 166:489–495
6. Watkins JM, Asarnow RF, Tanguay PE: Symptom development in childhood-onset schizophrenia. J Child Psychol Psychiatry 1988; 29:865–878
7. Frazier JA, Giedd JN, Hamburger SD, Albus KE, Kaysen D, Vaituzis AC, Rajapakse JC, Lenane MC, McKenna K, Jacobsen LK, Gordon CT, Breier A, Rapoport JL: Brain anatomic magnetic resonance imaging in childhood-onset schizophrenia. Arch Gen Psychiatry 1996; 53:617–624
8. Jacobsen LK, Giedd JN, Vaituzis AC, Hamburger SD, Rajapakse JC, Frazier JA, Kaysen D, Lenane MC, McKenna K, Gordon CT, Rapoport JL: Temporal lobe morphology in childhood-onset schizophrenia. Am J Psychiatry 1996; 153:355–361
9. Fennig S, Putnam K, Bromet EJ, Galambos N: Gender, premorbid characteristics and negative symptoms in schizophrenia. Acta Psychiatr Scand 1995; 92:173–177
10. Flaum M, Swayze VW II, O'Leary DS, Yuh WTC, Ehrhardt JC, Arndt SV, Andreasen NC: Effects of diagnosis, laterality, and gender on brain morphology in schizophrenia. Am J Psychiatry 1995; 152:704–714
11. Kendler KS, Walsh D: Gender and schizophrenia: results of an epidemiologically-based family study. Br J Psychiatry 1995; 167: 184–192
12. Haas GL, Sweeney JA: Premorbid and onset features of first-episode schizophrenia. Schizophr Bull 1993; 18:373–386
13. Flaum M, Arndt S, Andreasen NC: The role of gender in studies of ventricle enlargement in schizophrenia: a predominantly male effect. Am J Psychiatry 1990; 147:1327–1332
14. Weinberger DR, Cannon-Spoor E, Potkin SG, Wyatt RJ: Poor premorbid adjustment and CT scan abnormalities in chronic schizophrenia. Am J Psychiatry 1980; 137:1410–1413
15. Murray RM, Reveley AM, Lewis SW: Family history, obstetric complications and cerebral abnormality in schizophrenia, in Handbook of Schizophrenia, vol 3: Nosology, Epidemiology, and Genetics. Edited by Tsuang MT, Simpson JC. New York, Elsevier, 1988, pp 563–577
16. Andreasen NC, Olsen SA, Dennert JW, Smith MR: Ventricular enlargement in schizophrenia: relationship to positive and negative symptoms. Am J Psychiatry 1982; 139:297–302
17. Pearlson GD, Garbacs DJ, Breakey WR, Ahn HS, Depaulo JR: Lateral ventricular enlargement associated with persistent unemployment and negative symptoms in both schizophrenia and bipolar disorder. Psychiatry Res 1984; 12:1–9
18. Swayze VW II, Andreasen NC, Alliger RJ, Yuh WT, Ehrhardt JC: Subcortical and temporal structures in affective disorder and schizophrenia: a magnetic resonance imaging study. Biol Psychiatry 1992; 31:221–240
19. Andreasen NC, Flashman L, Flaum M, Arndt S, Swayze V II, O'Leary DS, Ehrhardt JC, Yuh WTC: Regional brain abnormalities in schizophrenia measured with magnetic resonance imaging. JAMA 1994; 272:1763–1769
20. Jones PB, Harvey I, Lewis SW, Toone BK, Van Os J, Williams M, Murray RM: Cerebral ventricle dimensions as risk factors for schizophrenia and affective psychosis: an epidemiological approach to analysis. Psychol Med 1994; 24:995–1011
21. Bilder RM, Wu H, Bogerts B, Wilson D, Liberman JA: Brain vol-

ume correlated with neuropsychological ability in first-episode schizophrenia, in Abstracts of the 50th Annual Meeting of the Society of Biological Psychiatry. Los Angeles, SBP, 1995
22. Jones PB, Owen MJ, Lewis SW, Murray RM: A case-control study of family history and cerebral cortical abnormalities in schizophrenia. Acta Psychiatr Scand 1993; 87:6–12
23. D'Amato T, Rochet T, Dalery J, Laurent A, Chauchat J-H, Terra J-L, Marie-Cardine M: Relationship between symptoms rated with the Positive and Negative Syndrome Scale and brain measures in schizophrenia. Psychiatry Res 1992; 44:55–62
24. Johnstone EC, Bruton CJ, Crow TJ, Frith CD, Owens DGC: Clinical correlates of postmortem brain changes in schizophrenia: decreased brain weight and length correlate with indices of early impairment. J Neurol Neurosurg Psychiatry 1994; 5:474–479
25. Buchanan RW, Carpenter WT: Domains of psychopathology: an approach to the reduction of heterogeneity in schizophrenia. J Nerv Ment Dis 1994; 182:193–204
26. Johnstone EC, Frith CD, Lang FH, Owens DG: Determinants of the extremes of outcome in schizophrenia. Br J Psychiatry 1995; 167:604–609
27. Bettes B, Walker E: Positive and negative symptoms in psychotic and other psychiatric disturbed children. J Child Psychol Psychiatry 1987; 28:555–568
28. Lewis SW, Owen MJ, Murray RM: Obstetric complications in schizophrenia: methodology and mechanisms, in Schizophrenia: Scientific Progress. Edited by Schulz SC, Tamminga CA. New York, Oxford University Press, 1989, pp 56–68
29. Lewine RRJ: Sex differences in schizophrenia: timing or subtypes? Psychol Bull 1981; 90:432–444
30. McKenna K, Gordon CT, Lenane M, Kaysen D, Rapoport JL: Looking for childhood-onset schizophrenia: the first 71 cases screened. J Am Acad Child Adolesc Psychiatry 1994; 33:636–644
31. Giedd JN, Kozuch P, Kaysen D, Vaituzis CA, Hamburger SD, Bartko JJ, Rapoport JL: Reliability of cerebral measures in repeated examinations with magnetic resonance imaging. Psychiatry Res Neuroimaging 1995; 61:113–119
32. Cannon-Spoor HE, Potkin SG, Wyatt RJ: Measurement of premorbid adjustment in chronic schizophrenia. Schizophr Bull 1982; 8:470–484
33. Lord C: Methods and measures of behavior in the diagnosis of autism and related disorders. Psychiatr Clin North Am 1991; 14:69–80
34. Overall JE, Gorham DR: The Brief Psychiatric Rating Scale. Psychol Rep 1962; 10:799–812
35. Andreasen NC: Scale for the Assessment of Negative Symptoms (SANS). Iowa City, University of Iowa, 1984
36. Andreasen NC: Scale for the Assessment of Positive Symptoms (SAPS). Iowa City, University of Iowa, 1984
37. Zax M, Sameroff AJ, Babigian HM: Birth outcome in the offspring of mentally disordered women. Am J Orthopsychiatry 1977; 47:218–230
38. Snell JV, Merickel MB, Ortega JM, Goble JC, Brookeman JR, Kassell NJ: Model-based boundary estimation of complex objects using hierarchical active surface templates. J Pattern Recognition 1995; 28:1599–1609
39. Giedd JN, Snell JW, Lange N, Rajapakse JC, Casey BJ, Kozuch PL, Vaituzis C, Vauss YC, Hamburger SD, Kaysen D, Rapoport JL: Quantitative magnetic resonance imaging of human brain development: ages 4–18. Cereb Cortex 1996; 6:551–560
40. Andreasen NC, Flaum M, Swayze V II, O'Leary DS, Alliger R, Cohen G, Ehrhardt J, Yuh WT: Intelligence and brain structure in normal individuals. Am J Psychiatry 1993; 150:130–134
41. Lim KO, Harris D, Beal M, Hoff AL, Minn K, Csernansky JG, Faustman WO, Marsh L, Sullivan EV, Pfefferbaum A: Gray matter deficits in young-onset schizophrenia are independent of age of onset. Biol Psychiatry 1996; 40:4–13
42. Rubin P, Hemmingsen R, Holm S, Moller-Madsen S, Hertel C, Povlsen UJ, Karle A: Relationship between brain structure and function in disorders of the schizophrenic spectrum: single position emission computed tomography, computed tomography and psychopathology of first episodes. Acta Psychiatr Scand 1994; 90:281–289
43. Selemon LD, Rajkowska G, Goldman-Rakic P: Abnormally high neural density in the schizophrenic cortex: a morphometric analysis of prefrontal area 9 and occipital area 17. Arch Gen Psychiatry 1995; 52:805–818
44. Tracy JI: Nonspecific abnormalities in psychiatry: do they reflect an ordered pathway of brain dysfunction? Biol Psychiatry 1995; 38:207–209